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PATENT SPECIFICATION

NO DRAWINGS

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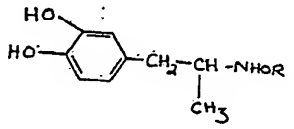
COMPLETE SPECIFICATION

3,4-Dihydroxyphenyl-Propane Derivatives

We, LEPETIT S.P.A., an Italian Body Corporate of Via Roberto Lepetit 8, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with new hypertensive agents. More particularly, the compounds with which the invention is concerned are 3,4-dihydroxyphenylpropane derivatives of the formula



wherein R represents hydrogen or a lower alkyl group of 1—8 carbon atoms inclusive, and their addition salts with aliphatic mono- and di-carboxylic acids

The compounds of this invention display a very high degree of hypertensive activity, which is superior to that of well known and therapeutically widespread agents.

The following Table gives a comparison of the increase in arterial pressure caused by some representatives of this class and *p*-hydroxy-α-(methylaminomethyl)-benzyl alcohol at intravenous doses of 0.5 and 1 mg/Kg. in cats under anaesthesia with chloralose urethane.

Compound (generic formula)	dose mg/Kg.	% increase in pressure (mm.Hg.)	duration of effect in min.
R=			
H	0.5	41	10
	1	72	13
CH_3	0.5	28	9
	1	42	10
C_2H_5	0.5	20	8
	1	40	10
p-hydroxy-α-(methylamino-methyl)-benzyl alcohol	0.5	12	4.5
	1	34	5

[*Price 4s. 6d.*]

Still more apparent results were observed in experiments on rats, by recording the % increase of pressure as measured at the tail after 10 minutes from intraperitoneal administration of 10 mg/Kg. The figures recorded were as follows:—

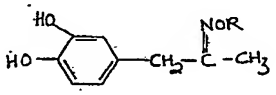
Compound R=	% increase in pressure (mm. Hg)
H	49.1
CH_3	38.6
C_2H_6	35.5
p-hydroxy-α-(methylamino-methyl)-benzyl alcohol	11.0

The acute toxicity in rats and mice was reasonably low, and in any case not higher than that of *p*-hydroxy-α-(methylaminomethyl)-benzyl alcohol.

For therapeutic purposes the compounds are best administered in the form of their salts with aliphatic mono- and di-carboxylic acids. In this respect, oxalic, malonic and succinic acids have proven to give salts particularly apt for practical purposes of administration.

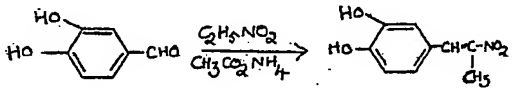
The invention therefore provides a therapeutic composition comprising as the active ingredient a compound of the above general formula or an addition salt thereof with an aliphatic mono- or di-carboxylic acid together with a pharmaceutically acceptable carrier.

The process for preparing the new hypertensive agents consists in subjecting a 3,4-dihydroxybenzyl-methyl ketone oxime of the general formula:



in which R has the above significance, to hydrogenation at room temperature and atmospheric pressure in a mixture of concentrated aqueous hydrochloric acid and a lower aliphatic alcohol of 1 to 8 carbon atoms inclusive, using platinum oxide as the catalyst.

The starting ketone oxime can be prepared in turn by different routes. For instance, 3,4-dihydroxybenzyl-methyl-ketone may be converted to the oxime by conventional procedures such as treatment with hydroxylamine or a substituted hydroxylamine NH_2OR. Alternatively, protocatechualdehyde may be condensed with nitroethane in the presence of ammonium acetate to give 3,4-dihydroxy-1-(2-nitro-1-propenyl)-benzene:



which latter compound is then hydrogenated to give the oxime. For better illustration, the Examples include also preparation of the starting oximes.

The following non-limitation Examples illustrate the process and products of the present invention.

EXAMPLE 1.

1-(3,4-Dihydroxyphenyl)-2-hydroxyaminopropane.

To a solution of 144 g. of protocatechualdehyde in 3000 ml. of nitroethane, heated to about 90°C, 14 g. of ammonium acetate are gradually added, the the mixture is heated at 100°C for 3 hours. The excess nitroethane is then distilled off. The residue is 1-(3,4-dihydroxyphenyl)-2-nitroproplene, m.p. 148—149°C. Yield 192 g. (94%).

Into a mixture of 180 g. of 1-(3,4-dihydroxyphenyl)-2-nitroproplene, 1000 ml. of

methanol, 750 ml. of water and 300 ml. of about 12% aqueous hydrochloric acid, in the presence of 18 g. of 10% palladium on charcoal, hydrogen is bubbled until absorption practically ceases. The mixture is filtered and the filtrate is concentrated to a volume of about 1000 ml. and extracted with ethyl acetate. On evaporation of the solvent, 131 g. (78%) of 3,4-dihydroxybenzyl methyl ketone oxime are obtained, with m.p. 145—148°C.

A mixture of 36.2 g. of 3,4-dihydroxybenzyl methyl ketone oxime, 3.7 g. of platinum oxide, 19.5 ml. of concentrated hydrochloric acid and 750 ml. of butanol is hydrogenated at room temperature until no more hydrogen is absorbed. The mixture is made neutral by the addition of sodium bicarbonate, and about 150 g. of sodium sulphate are added and the mixture is filtered. To the filtrate, a solution of 11.5 g. of succinic acid in 100 ml. of butanol are added, the solution is concentrated to a volume of about 100 ml. and cooled. The succinate of 1-(3,4-dihydroxyphenyl)-2-hydroxaminopropane precipitates and is collected and dried. Yield 27 g., m.p. 157—159°C.

From the succinate the free hydroxamino compound can be obtained by treatment with aqueous sodium bicarbonate, extraction with diethyl ether and evaporation to dryness of the solvent. The product has m.p. 120—123°C.

EXAMPLE 2.

1-(3,4-Dihydroxyphenyl)-2-methoxaminopropane.

A solution of 33.2 g. of 3,4-dihydroxybenzyl methyl ketone in 300 ml. of ethanol is admixed with a solution of 16.6 g. of O-methylhydroxylamine hydrochloride and 16.4 g. of sodium acetate in 50 ml. of water and allowed to stand for 3 days at room temperature. The solution is then evaporated to dryness and the residue recrystallised from benzene. Yield 35 g. of 3,4-dihydroxybenzyl methyl ketone methoxime, m.p. 110—112°C, b.p. 140—150°C/0.2 mm.

A mixture of 30 g. of the above methoxime, 3 g. of platinum oxide, 12.5 ml. of concentrated hydrochloric acid and 1000 ml. of ethanol is hydrogenated as described in Example 1. The mixture is filtered, the filtrate is evaporated to dryness. The residue is recrystallised from isopropanol. Yield 28.8 g. (80%) of 1-(3,4-dihydroxyphenyl)-2-methoxaminopropane, m.p. 155—158°C.

EXAMPLE 3.

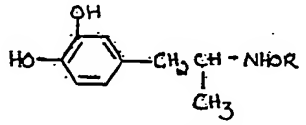
1-(3,4-Dihydroxyphenyl)-2-ethoxaminopropane.

A mixture of 13.28g. of 3,4-dihydroxybenzyl methyl ketone, 7.76 g. of N-ethylhydroxylamine, 6.56 g. of sodium acetate and 220 ml. of 90% ethanol is allowed to stand at room temperature for 2 days, then it is evaporated to dryness. The residue is dissolved in diethyl ether, filtered and evaporated to dryness. The residue is recrystallised from benzene and is 3,4-dihydroxybenzyl methyl ketone ethoxime, m.p. 126—128°C.

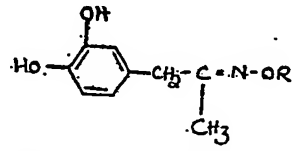
The ethoxime is hydrogenated by the process described in the foreging Examples and gives a 76% yield of 1-(3,4-dihydroxyphenyl)-2-ethoxaminopropane, m.p. 146—148°C (from isopropanol).

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the general formula:—

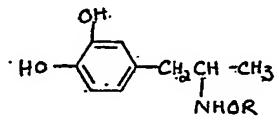


wherein R is a hydrogen or a lower alkyl group of 1—8 carbon atoms inclusive, which comprises subjecting a compound of the general formula:—



wherein R has the above significance, to hydrogenation in a mixture of concentrated aqueous hydrochloric acid and a lower aliphatic alcohol of 1 to 8 carbon atoms inclusive, at room temperature and atmospheric pressure, in the presence of platinum oxide.

2. A 3,4-dihydroxyphenylpropane derivative of the general formula:—



wherein R is hydrogen or a lower alkyl group of 1—8 carbon atoms inclusive, and addition salts thereof with mono- and di-carboxylic acids.

3. 1-(3,4-Dihydroxyphenyl)-2-hydroxaminopropane.

4. 1-(3,4-Dihydroxyphenyl)-2-hydroxaminopropane succinate.

5. 1-(3,4-Dihydroxyphenyl)-2-methoxaminopropane.

6. 1-(3,4-Dihydroxyphenyl)-2-ethoxaminopropane.

7. A process for the preparation of a compound as claimed in any of claims 2 to 6 substantially as herein described with reference to the Examples.

8. A compound as claimed in any of claims 2 to 6 when prepared by a process as claimed in claim 1 or 7.

9. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 2 to 6 or 8 together with a pharmaceutically acceptable carrier.

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